PATENT COOPERATION TREATY

- 9 APR 2001

From the
INTERNA. ONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	05.04.2001
Applicant's or agent's file reference AHB/CP5852983	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/01679	02/05/2000	30/04/1999

Applicant
CAMBRIDGE ANTIBODY TECHNOLOGY LIMITED et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Digiusto, M Tel.+49 89 2399-8162

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
AHB/CP5852983		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/01679	02/05/2000	30/04/1999
International Patent Classification (IPC) or national classification and IPC C07K16/22		
Applicant CAMBRIDGE ANTIBODY TECHNOLOGY LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26/10/2000	05.04.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer von Ballmoos, P Telephone No. +49 89 2399 8174

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERN. IONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/01679

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-57	as originally filed				

Claims, No.:

1-25	as originally filed				
26,27	as received on	06/03/2001	with letter of	06/03/2001	

Drawings, sheets:

1/9-9/9	as originally filed				

Sequence listing part of the description, pages:

1-2, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☒ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☒ furnished subsequently to this Authority in computer readable form.

   ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☒ The statement that the information recorded in computer readable form is identical to the written sequence

listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:
   see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 21-22 with respect to industrial applicability.

because:

   ☒ the said international application, or the said claims Nos. 21-22 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-27
	No:	Claims	---
Inventive step (IS)	Yes:	Claims	1-25
	No:	Claims	26-27
Industrial applicability (IA)	Yes:	Claims	1-20, 23-27
	No:	Claims	---

2. Citations and explanations
see separate sheet

Part III

Claims 21-22 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Part V

Reference is made to the following document:

D1 WO 9713844

Part Va) Novelty and Inventive step

The closest prior art is represented by D1. This document describes the process of selecting antibodies with specificity to TGFβ1. The most potent neutralising antibody is CS37 (see e.g. example 9) which has exceptionally good properties compared to the other antibodies (7A3, 10A6, 14A1, CS32, CS39, 31G9).

The percentage of identity between the heavy or light chains of the CS37 antibody and the antibody of the present invention is as follows:

a) SL15 VH (SEQ ID NO: 4) of the present invention is distinguished from the D1 VH chains (VH of CS37) by selection of CDR3 having the sequence SEQ ID NO:13 and has 93.5% sequence identity in a 123aa overlap with the D1 VH chain (see D1, claim 16, Fig. 1a(i) and Fig. 1a(ii)); see also p. 5, Table 2 of the present application.

b) JT182 VH (SEQ ID NO:10) of the present invention is distinguished from the D1 VH chains (VH of CS37) by selection of CDR3 having the sequence SEQ ID NO:15 and has 94% sequence identity in a 124aa overlap with the D1 VH chain (see D1, claim 16, Fig. 1a(i) and Fig. 1a(ii)); see also p. 5, Table 2 of the present

application.

c) SL15A VL (SEQ ID NO:6) is identical to the D1 VL chains (VL of CS37) (see D1, claim 22, Fig. 14); see also present application, p. 43, l. 6-10.

d) SL15S VL (SEQ ID NO: 8) is distinguished from the D1 VL chain (VL of CS37) by selection of CDR1 having the sequence SEQ ID NO:19 and has 99% sequence identity in a 107aa overlap with the D1 VL chain(see D1, claim 22, Fig. 14); see also p. 5, Table 2 of the present application.

1. Independent claims 1, 5-8

Independent claims 1, 5-8, which all relate to antibodies including one or more of the novel sequences are novel and meet the requirements of Art. 33(2) PCT.
Furthermore, the experiments in the application show that the use of the novel CDR3 sequences in the VH chain (sequences with SEQ ID NO. 4, 13, 10, 15) leads to a huge increase in antibody activity compared to antibody CS37 (see e.g. Table 1).
The same applies to the novel sequences SEQ ID NO: 8 and SEQ ID NO: 19 of the light chain which also contribute to the improvement of the known CS37 antibody (see experiments relating to SL15S antibodies which include these novel light chain sequences, e.g. Fig. 2). The finding of heavy and light chain sequences which improve the excellent properties of CS37 even more (see the factor 100-150 between activity of CS37 antibody and antibodies according to present invention, Table 1) is a surprising effect and the skilled person would not have had an incentive to develop these antibody sequences.

Hence, presence of an inventive step is acknowledged for independent claims 1, 5-8 (Art. 33(3) PCT).

2. Independent claims 13, 14, 21, 23, 24, 25

Independent claims 13, 14, 21 and 23 relate to the use of the novel and inventive antibodies in methods of treating a patient or in methods of diagnosing TGFβ1 and

claims 24 and 25 relate to the nucleic acid encoding the novel and inventive antibodies. Hence, these claims also meet the requirements of Art. 33(2) and Art. 33(3) PCT.

3. Dependent claims 2-4, 9-12, 15-20 and 22

Dependent claims 2-4, 9-12, 15-20 and 22 contain preferred embodiments of the novel and inventive idea and would also appear to meet the requirements of Articles 33(2) and 33(3) PCT.

4. Amended claims 26 and 27

Due to their wording, both claims encompass an embodiment which relates to a method of obtaining an antibody for TGFβ1 by mutating the sequence identified as SEQ ID NO:6 (see claim 26) or identified as JT182 VL CDR3 (see claim 27). However, SEQ ID NO:6 is identical to the known VL sequence of antibody CS37 (compare SEQ ID NO.6 with Figure 14 in D1) and JT182 VL CDR3 corresponds to the CDR3 of CS37 VL.
Hence, claims 26 and 27 encompass a method of preparing novel TGFβ1 antibodies by mutating the known CS37 antibody. Methods of modifying a known antibody in order to create more potent derivatives, however, is standard in the art. Hence, claims 26 and 27 do not involve an inventive step, contrary to Art. 33(3) PCT.

Part Vb) Industrial applicability

For the assessment of the present claims 14-22 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

26. A method for obtaining an antibody antigen binding domain specific for TGFβ_1, the method comprising

providing by way of addition, deletion, substitution or insertion of one or more amino acids in the amino acid sequence of a VH domain selected from SEQ ID NO. 4 and SEQ ID NO. 10 a VH domain which is an amino acid sequence variant of the VH domain, and combining the VH domain thus provided with one or more VL domains to provide one or more VH/VL combinations; and/or

providing by way of addition, deletion, substitution or insertion of one or more amino acids in the amino acid sequence of a VL domain selected from SEQ ID NO. 6 and SEQ ID NO. 8 a VL domain which is an amino acid sequence variant of the VL domain, and combining the VL domain thus provided with one or more VH domains to provide one or more VH/VL combinations;

and

testing the VH/VL combination or combinations to identify an antibody antigen binding domain specific for TGFβ_1.

27. A method of preparing a specific binding member specific for TGFβ_1, which method comprises:

providing a starting repertoire of nucleic acids encoding a VH domain which either include a CDR3 to be replaced or lack a CDR3 encoding region;

combining said repertoire with a donor nucleic acid encoding an amino acid sequence substantially as set out herein for SL15 or JT182 VH CDR3 such that said donor nucleic acid is inserted into the CDR3 region in the repertoire, so as to provide a product repertoire of nucleic acids encoding a VH domain; and/ or

providing a starting repertoire of nucleic acids encoding a VL domain which either include a CDR3 to be replaced or lack a CDR3 encoding region;

combining said repertoire with a donor nucleic acid encoding an amino acid sequence substantially as set out herein for SL15 or JT182 VL CDR3 such that said donor nucleic acid is inserted into the CDR3 region in the repertoire, so as to provide a product repertoire of nucleic acids encoding a VL domain;

and

expressing the nucleic acids of said product repertoire;

selecting a specific binding member specific for $TGF\beta_1$; and

recovering said specific binding member or nucleic acid encoding it.